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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/555,629	07/31/2001	Naoki Yamazaki	2520-0118P	1386

2292 7590 07/03/2003

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EXAMINER
BUNNER, BRIDGET E

ART UNIT	PAPER NUMBER
1647	13

DATE MAILED: 07/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/555,629	YAMAZAKI ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-5* is/are allowed.

6)☒ Claim(s) *6 and 7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-7* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 31 July 2001 (Paper No. 8) has been entered in full. Claims 1 and 10 are amended.

Election/Restrictions

Applicant's election with traverse of Groups I and II in Paper No. 12 (02 April 2003) is acknowledged. The traversal is on the ground(s) that Groups I and II are linked as forming a single general inventive concept under PCT Rule 13.1. Applicant argues that the special technical feature of this invention is a preparation containing hepatocyte growth factor for continuous intravenous administration. This is not found persuasive. As discussed in the previous Office Action (Paper No. 10, 02 October 2002), claims 1-5 are anticipated by Kawaida et al. (Proc Natl Acad Sci USA 91: 4537-4361, 1994). Claim 1 lacks a special technical feature and cannot share one with the other claims. Furthermore, the product claimed can be used in materially different processes, such as for the production of antibodies or for the treatment of other unrelated diseases, such as hypertension or cardiovascular disease.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-5 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected group, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 12 (02 April 2003).

Claims 6-7 are under consideration in the instant application.

Information Disclosure Statement

1. The information disclosure statement filed 31 July 2001 (Paper No. 9) fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It is noted to Applicant that copies of document A449246 Japan, Kawa et al., and Kunio Matsunaga et al. are requested by the Examiner. Applicant must submit copies of these three documents and a new PTO-1449 form that lists the documents so they can be initialed by the Examiner.

2. The information disclosure statement filed 31 July 2001 (Paper No. 9) fails to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of each patent/reference listed that is not in the English language. It has been placed in the application file, but the information referred to therein has not been considered. It is noted to Applicant that the document A449246 Japan, Kawa et al., and Kunio Matsunaga et al. are most likely in Japanese. Therefore, an explanation of the relevance of each citation in English is requested by the Examiner. Although Kawa et al. has an abstract in English, Applicant is requested to provide greater explanation of the article in English.

Specification

2. The disclosure is objected to because of the following informalities:

2a. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: "METHOD FOR TREATMENT OF ACUTE RENAL FAILURE BY ADMINISTRATION OF HEPATOCYTE GROWTH FACTOR".

Appropriate correction is required.

Claim Objections

3. Claims 6-7 are objected to because of the following informalities:

3a. Claims 6-7 (lines 2) recite "administrating" instead of "administering".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 6 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating acute renal failure comprising administering an effective amount of hepatocyte growth factor (HGF) by continuous intravenous administration to a patient suffering from acute renal failure, does not reasonably provide enablement for a method for treating or preventing renal disease which comprises adminstrating an effective amount of HGF by continuous intravenous administration. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claim is directed to a method of treating or preventing renal disease which comprises administering an effective amount of HGF by continuous intravenous administration.

The specification teaches that renal injury models by nephrotoxins, such as mercury II chloride ($HgCl_2$), present acute tubulorrhexis which is a pathology of acute renal failure, have been traditionally used as disease models of acute renal failure (pg 2, lines 6-10). It is noted that the specification and relevant art do not disclose that the administration of $HgCl_2$ to animals is a model for any other renal disease, other than acute renal failure. The specification also discloses that BALBc/mice are administered $HgCl_2$. A half hour later the mice are given either vehicle (control) or HGF at various concentrations via continuous intravenous administration (pg 12 through the top of pg 17; Figures 3-12). The specification also teaches that there is a significant decrease in BUN and creatinine levels with an HGF dose of 200 μg/kg/day for a period of administration of 5 hours (pg 13 to top of pg 14; Figure 6). There is also a significant decrease in BUN and creatinine levels with an HGF dose of 180 μg/kg/day and 600 μg/kg/day for a period of administration of 3 hours (pg 16-17; Figure 12). However, the specification does not teach treating any renal diseases with HGF, other than acute renal failure. The phrase "renal disease" in the claim is interpreted by the Examiner to be broad, in that it encompasses any and all kidney diseases or disorders. The specification even discloses that examples of renal diseases include acute renal failure, systemic lupus erythematosus, diabetic nephropathy, kidney transplant, nephro-urinary tumor, and drug-induced renal disorder, among others (pg 8, lines 12-22). These various renal diseases and disorders disclosed in the specification have different pathophysiologies. For example, acute renal failure is the rapid breakdown of renal function that occurs when high levels of uremic toxins accumulate in the blood. Acute renal failure occurs when the kidneys are unable to excrete the daily load of toxins in the urine (Singri et al. J Am Med Assoc 289(6): 747-751, 2003; pg 747). Systemic lupus erythematosus is a chronic

rheumatic disease with many clinical presentations, which may lead to inflammation and damage to various body organs (Ioannou et al., Postgrad Med J 78: 599-606, 2002; pg 599, abstract, col 1). The mechanisms causing the disease are still unknown (Ioannou et al., pg 599, ¶ 3). Undue experimentation would be required of the skilled artisan to continuously administer HGF to individuals with all possible renal diseases disorders and successfully treat the disorder. One skilled in the art would also not be able to predict from the of the instant specification that HGF would be able to treat all possible renal diseases, such as acute renal failure and systemic lupus erythematosus, because renal diseases have different pathophysiologies.

Additionally, the claim does not specify what specific effect the "effective amount" of HGF has. Undue experimentation would be required of the skilled artisan to determine the effect of HGF after administration to a subject. Also, the claim does not define a patient population. The Examiner has interpreted the claim to mean that any subject or population, healthy or diseased, can be administered HGF to treat or prevent any renal disease. A large quantity of experimentation would be required by one skilled in the art to treat or prevent all possible renal diseases in all possible subjects.

Furthermore, the specification also does not disclose preventing any renal disease by administration of HGF in any animal. The term "prevent" is interpreted as meaning that an activity will not occur, i.e. renal disease will not occur. The results and figures in the specification only disclose that creatinine and BUN levels (parameters of renal disease) are significantly reduced (see for example, Example 2, parts 2 and 4; Example 3; Figures 5-6, 9-12). Undue experimentation would be required of the skilled artisan to determine the quantity of HGF

administered, the best route of administration, the duration of treatment, and any possible side-effects to prevent renal disease in a subject.

Due to the large quantity of experimentation necessary to treat and prevent all possible renal diseases by administration of HGF to all possible subjects and to determine what effect an "effective amount" of HGF has, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, and the unpredictability of the effects of administration of HGF for all possible renal diseases to all possible subjects (see discussion), undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

5. Claim 7 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claim is directed to a method for treating or preventing occlusive lesion of blood vessel which comprises administrating an effective amount of HGF by continuous intravenous administration.

The specification teaches that in the glycerol model for administering glycerol in muscles, it is accompanied by injury of skeletal muscles, release of myoglobin from skeletal muscles into the blood, and release of creatine kinase, creatine, potassium, phosphoric acid, and purine precursor into the blood (pg 4, lines 13-18). The specification discloses that the glycerol model is regarded as the so-called MNMS (myonephropathic-metabolic syndrome) model, such

as rhabdomyolysis, myoglobinuria, and detrition syndrome that are accompanied by decay of skeletal tissues (pg 4, lines 18-21). The specification also teaches that if ischemia continues due to acute vascular occlusion, ischemic muscular necrosis widely occurs and MNMS that elevates levels of creatine kinase, potassium, and myoglobin in serum, is induced (pg 4, lines 23-26). The specification concludes that therefore, the glycerol model is also regarded as a model of occlusive lesion of blood vessel (pg 4, lines 26-28). However, relevant literature indicates that the glycerol model is not utilized as model for MNMS or occlusive lesion of blood vessels, but rather for acute renal failure (Kudo et al., U.S. Patent 6,436,388, col 2, lines 27-44). Additionally, the art teaches that MNMS, for example, may induced by ischemia (Tsuji et al. Eur J Vasc Surg 8: 484-488, 1994, abstract, pg 482-483 ; Hayashi, S. Kurume Med J 47(1) : 63-72, 2000 ; abstract).

The specification teaches that Wistar rats are administered glycerol. Eight hours afterward, an intravenous administration of HGF or bolus injection of HGF is given (pg 17, lines 12-19). The specification teaches that on the 11th day after the glycerol injection, the survival rate in the control group is 2/8 and 8/10 in the HGF by continuous administration, wherein HGF significantly increases survival (pg 17, lines 21-24). Regarding the bolus group, the survival rate in the control group is 5/8 and 5/8 in the HGF group, wherein no life-saving effect of HGF is recognized (pg 17, lines 24-26). However, the specification does not treat occlusive lesion of blood vessel with HGF. The phrase "occlusive lesion of blood vessel" in the claim is interpreted by the Examiner to be broad, in that it encompasses numerous diseases and disorders with occlusive lesion of blood vessel. The specification even discloses that examples of occlusive lesion of blood vessel include lower limb ischemia, arterial embolism, arterial thrombosis,

Buerger's disease, and pulmonary embolism among others (pg 8, lines 23-28). However, the various disorders disclosed in the specification have different pathophysiologies. For example, arterial embolism is a sudden interruption of blood flow to an organ or body part, caused when the artery that supplies the blood to that organ or body part is blocked by an embolus (blood clot or atherosclerotic plaque) (see Medline Plus health information; http://www.nlm.nih.gov/medlineplus/ency/article/001102.htm; Appendix A). Buerger's disease is an acute inflammation and thrombosis of arteries and veins, with symptoms including claudication (pain induced by insufficient blood flow during exercise) in the feet and/or hands, or pain in these areas at rest (The Johns Hopkins Vasculitis Center, http://vasculitis.med.jhu.edu/typesof/buergers.html; Appendix B). Undue experimentation would be required of the skilled artisan to continuously administer HGF to individuals with all possible disorders that cause or are associated with occlusive lesion of blood vessel and successfully treat the disorder. One skilled in the art would also not be able to predict from the of the instant specification that HGF would be able to treat all possible disorders that cause or are associated with occlusive lesion of blood vessel, such as arterial embolism or Buerger's disease, because occlusive lesion of the blood vessel encompasses many diseases and disorders which have different pathophysiologies.

Furthermore, claim 7 does not specify what specific effect the "effective amount" of HGF has. Undue experimentation would be required of the skilled artisan to determine the effect of HGF after administration to a subject. Also, the claim does not define a patient population. The Examiner has interpreted the claim to mean that any subject or population, healthy or diseased, can be administered HGF to treat or prevent any occlusive lesion of blood vessel. A large

quantity of experimentation would be required by one skilled in the art to treat or prevent all possible diseases or disorders with occlusive lesion of blood vessel in all possible subjects.

Additionally, the specification does not disclose preventing occlusive lesion of blood vessel by administration of HGF in any animal. The term "prevent" is interpreted as meaning that an activity will not occur, i.e. occlusive lesion of blood vessel will not occur. Undue experimentation would be required of the skilled artisan to determine the quantity of HEGF administered, the best route of administration, the duration of treatment, and any possible side-effects to prevent occlusive lesion of blood vessel in a subject.

Due to the large quantity of experimentation necessary to treat and prevent all possible diseases and disorders with occlusive lesion of blood vessel by administration of HGF to all possible subjects, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, the state of the art indicating that glycerol is not used as an animal model for MNMS or occlusive lesion of blood vessel, and the unpredictability of the effects of administration of HGF for all possible diseases or disorders with occlusive lesion of blood vessel to all possible subjects (see discussion), undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 6-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Regarding claims 6-7, the acronym "HGF" renders the claims vague and indefinite. Abbreviations should be spelled out in all independent claims for clarity.

8. Claims 6-7 are rejected as being indefinite because it is unclear to whom or to which patient population HGF is being administered to.

9. The term "occlusive lesion of blood vessel" in claim 7 is a relative term which renders the claim indefinite. The term "occlusive lesion of blood vessel" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear what physiological condition this term is referring to. For example, does "occlusive lesion of blood vessel" mean ischemia, necrosis, or blood clots, for example.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 6-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Kawa et al. (Jpn Pharmacol Therapy 24(Suppl 1): 149-152, 1996.

Kawa et al. teach that Sprague-Dawley rats are administered a continuous administration of HGF (100 μg/kg BW/day) (see pg 149, abstract). The body of claims 6-7 only recite

Conclusion

No claims are allowable.

The art made of record and not relied upon is considered pertinent to applicant's disclosure:

Amaike et al. Cytokine 8(5) : 387-394, 1996.

Mizuno et al. J Clin Invest 101 : 1827-1834, 1998.

Yaekashiwa et al. Am J Respir Crit Care Med 156 : 1937-1944, 1997.

Yamasaki et al. Nephron 90 : 195-205, 2002.

Yo et al. Kidney Int 53 : 50-58, 1998.

Humes et al. U.S. Patent No. 5,360,790

Roos et al. U.S. Patent No. 5,654,404

Roos et al. U.S. Patent No. 5,703,048

Bunting et al. U.S. Patent No. 6,133,234

Nakamura et al. EP 0462549

~~Marschang~~ Bunting et al. WO 97/12628

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:30-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 872-9305.

BEB

Art Unit 1647
June 20, 2003

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER

Appendix A

Print this page | Close this window

Medical Encyclopedia: Arterial embolism

URL of this page: http://www.nlm.nih.gov/medlineplus/ency/article/001102.htm

Definition

Arterial embolism is a sudden interruption of blood flow to an organ or body part. This is caused when the artery that supplies the blood to that organ or body part is blocked by an embolus (blood clot or atherosclerotic plaque) that has moved in the bloodstream from its point of origin to a new location.

The point of origin for the embolus can be the heart or a large blood vessel.

Causes, incidence, and risk factors

An embolus is a clot (or a piece of plaque that acts in the same manner as a clot) that travels from the site where it formed to another location in the body. The embolism can lodge in an artery at the new location and block the flow of blood there.

The blockage deprives the tissues in that location of its normal blood flow and oxygen (lack of blood and oxygen is called "ischemia"). This can result in damage or even death of the tissues (necrosis) in that organ.

Arterial embolism may be caused by a single embolus or multiple emboli.

Arterial emboli can affect the extremities -- especially the legs and feet. Some may involve the brain or heart, causing stroke or heart attack. Less common sites include the kidneys, gut (intestines), and the eyes.

A major risk for emboli is atrial fibrillation because the blood flow through the atria can be slow enough to trigger clots to form, which can then travel (embolize). The risk of an embolism increases when factors that tend to form clots are increased.

These may include injury or damage to an artery wall, hematologic (blood component) conditions associated with increased clotting (such as increased platelet count), and other disorders.

Another condition that poses a high risk for embolization (especially to the brain) is mitral stenosis. Endocarditis may also cause arterial emboli (paradoxical embolization), if a clot travels through a hole in the heart called (foramen ovale).

If an embolism involves the arteries supplying blood flow to the lungs, it is called not arterial embolism, but a pulmonary embolism, and it is a different condition (i.e., clots originated in the veins, not the arteries). Endocarditis can also cause pulmonary embolism.

Symptoms

EMBOLIZATION IN AN EXTREMITY

- muscle pain in the extremity (see knee pain, foot pain)

- numbness and tingling in the extremity
- pale color of arm or leg
- decreased or absent pulse in the extremity
- decreased extremity temperature, the extremity feels cold to touch
- lack of movement of the extremity
- weakness of the extremity
- muscle spasm in the extremity
- body feels cool (fingers or hands)
- muscle function loss

Symptoms may begin abruptly or slowly depending on the size of the embolus and the extent to which it blocks the blood flow.

Later symptoms:

- blisters develop easily
- skin erosion (ulcer)
- skin necrosis (skin is dark and damaged)
- skin falling off (sloughing)

EMBOLI IN AN INTERNAL ORGAN (see complications)

- Symptoms of ischemia (lack of oxygen) or infarction (tissue death): varies with organ involved. There may be pain and/or temporary decreased organ function.

Signs and tests

There may be decreased or absent pulse, and/or decreased or absent blood pressure in the extremity. There may be signs of tissue necrosis or gangrene.

Tests to diagnose arterial embolism or reveal the source of emboli may include:

- a Doppler ultrasound exam of an extremity
- transcranial Doppler
- echocardiography, transthoracic
- transesophageal echocardiography (TEE)
- myocardial contrast echocardiography (MCE)
- magnetic resonance imaging
- angiography of the affected extremity or organ
- renal arteriography
- extremity arteriography
- plethysmography
- a duplex Doppler/ultrasound exam of extremity

This disease may also alter the results of the following tests:

- isotope study
- platelet aggregation test
- factor VIII assay
- euglobulin lysis time (ELT)
- plasminogen activator inhibitor-1 (PAI-1) activity
- tissue-type plasminogen activator (t-PA) levels

Treatment

Arterial embolism requires prompt hospitalization for treatment. The goals of treatment are to control symptoms and to improve the interrupted blood flow to the affected area of the body. Intravenous analgesics are administered for pain control.

Medications that improve blood flow by breaking up the clot are local thrombolytics (such as streptokinase). The development of new clots is prevented with anticoagulants (such as warfarin or heparin) or antiplatelet medications (such as aspirin, ticlopidine, and clopidogrel).

Surgical procedures may be appropriate for some people. These may include thromboaspiration (clot aspiration), embolectomy (clot removal through a balloon catheter or through open surgery), angioplasty (dilatation of the artery with a balloon catheter) with or without implantation of a stent, and bypass of the blood vessel.

The underlying cause of the emboli, if identified, should be treated to prevent further embolization.

Expectations (prognosis)

The outcome varies depending on the location of the embolism and the extent that the embolism affects blood supply to the area. Arterial embolism can be serious if not treated promptly. It may be life-threatening, with a 25 to 30% death rate.

The affected area can be permanently damaged, with up to approximately 25% of cases requiring amputation of an affected extremity. Arterial emboli can recur even after successful treatment.

Complications

- infection in the affected tissue
- tissue death (necrosis) and gangrene of the extremity (See gas gangrene.) requiring amputation
- septic shock
- acute MI
- transient ischemic attack (TIA)
- stroke (CVA)
- temporary or permanent kidney failure
- temporary or permanent decrease/loss of other organ functions

Calling your health care provider

Go to the emergency room or call the local emergency number (such as 911) if symptoms indicate you may have an arterial embolism.

Prevention

Prevention of arterial embolization begins with prevention of the source of the embolus. For example, if a high risk for embolism is identified, blood thinners (such as Coumadin) may be prescribed to prevent formation of a blood clot that could be a source of the embolism.

Antiplatelet agents may also be needed. Measures to reduce atherosclerosis may reduce risk of an arterial embolus forming from a piece of atherosclerotic plaque. The risk for both atherosclerosis and clot formation/ embolism increases in persons who smoke, who are under stress, who are overweight, and who lead a sedentary life.

Update Date: 5/22/2002

Updated by: Elena Sgarbossa, M.D., Department of Cardiology, Rush-Presbyterian St. Luke's Medical Ctr., Chicago, IL. Review provided by VeriMed

Healthcare Network.

The information provided herein should

A.D.A.M., Inc. is accredited by URAC, also known as the American Accreditation HealthCare Commission (www.urac.org). URAC's accreditation program is the first of its kind, requiring compliance with 53 standards of quality and accountability, verified by independent audit. A.D.A.M. is among the first to achieve this important distinction for online health information and services. Learn more about A.D.A.M.'s editorial reviewers. A.D.A.M. is also a founding member of Hi-Ethics (www.hiethics.com) and subscribes to the principles of the Health on the Net Foundation (www.hon.ch).

Types of Vasculitis
Buerger's Disease

Appendix B

Behcet's Disease
Buerger's Disease
Central Nervous System Vasculitis
Churg-Strauss Syndrome
Cryoglobulinemia
Giant Cell Arteritis
Microscopic Polyangiitis
Polyarteritis Nodosa
Polymyalgia Rheumatica
Rheumatoid Vasculitis
Takayasu's Arteritis
Wegener's Granulomatosis

First Description

This disease was first reported by Buerger in 1908, who described a disease in which the characteristic pathologic findings — acute inflammation and thrombosis (clotting) of arteries and veins — affected the hands and feet. Another name for Buerger's Disease is *thromboangiitis obliterans.*

(top of page)

Who gets Buerger's Disease (the "typical" patient)?

The classic Buerger's Disease patient is a young male (e.g., 20–40 years old) who is a heavy cigarette smoker. More recently, however, a higher percentage of women and people over the age of 50 have been recognized to have this disease. Buerger's disease is most common in the Orient, Southeast Asia, India and the Middle East, but appears to be rare among African–Americans.

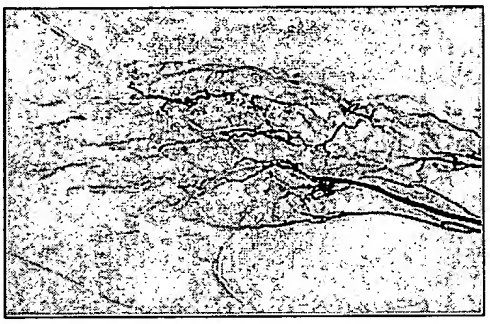
(top of page)

Classic symptoms and signs of Buerger's Disease

The initial symptoms of Buerger's Disease often include claudication (pain induced by insufficient blood flow during exercise) in the feet and/or hands, or pain in these areas at rest. The pain typically begins in the extremities but may radiate to other (more central) parts of the body. Other signs and symptoms of this disease may include numbness and/or tingling in the limbs and Raynaud's phenomenon (a condition in which the distal extremities — fingers, toes, hands, feet — turn white upon exposure to cold). Skin ulcerations and gangrene (**pictured below**) of the digits (fingers and toes) are common in Buerger's disease. Pain may be very intense in the affected regions.

An angiogram demonstrating lack of blood flow to vessels of the hand (**figure below**). This decreased blood flow ("ischemia") led to ulcers of the fingers and severe pain.

A normal angiogram of the hand (**figure below**).



Despite the severity of ischemia (lack of blood flow) to the distal extremities that occurs in Buerger's, the disease does not involve other organs, unlike many other forms of vasculitis. Even as ulcers and gangrene develop in the digits, organs such as the lung, kidneys, brain, and gastrointestinal (GI) tract remain unaffected. The reasons for the confinement to the extremities and sparing of other organs are not known.

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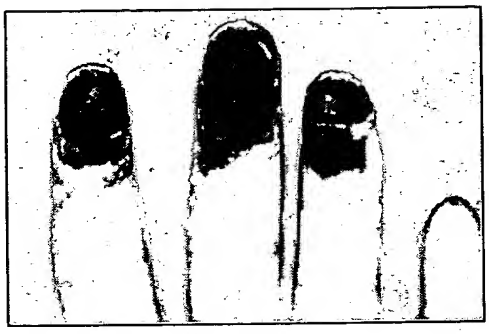
What Causes Buerger's Disease?

The association of Buerger's Disease with tobacco use, particularly cigarette smoking, cannot be overemphasized. Most patients with Buerger's are heavy smokers, but some cases occur in patients who smoke "moderately"; others have been reported in users of smokeless tobacco. It has been postulated that Buerger's Disease is an "autoimmune" reaction (one in which the body's immune system attacks the body's own tissues) triggered by some constituent of tobacco.

Pictured below, are a patient's fingertips that have developed gangrene. This is a very painful condition which sometimes requires amputation of the affected area.



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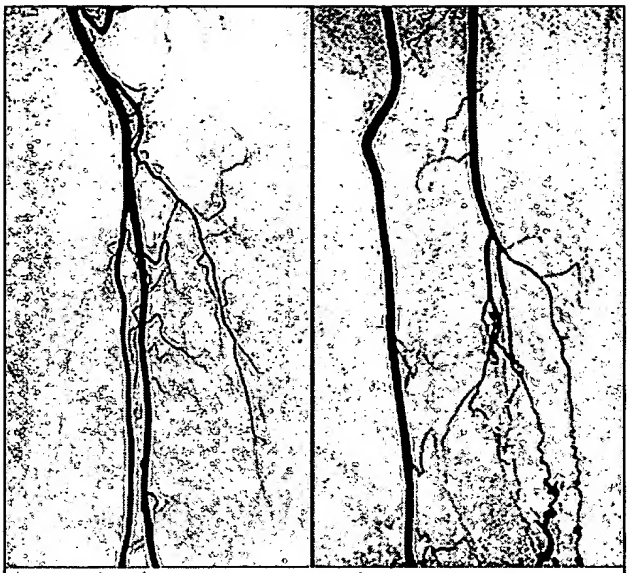
How is Buerger's Diagnosed?

Buerger's disease can be mimicked by a wide variety of other diseases that cause diminished blood flow to the extremities. These other disorders must be ruled out with an aggressive evaluation, because their treatments differ substantially from that of Buerger's Disease (for Buerger's, there is only one treatment known to be effective: complete smoking cessation — see below).

Diseases with which Buerger's Disease may be confused include atherosclerosis (build–up of cholesterol plaques in the arteries), endocarditis (an infection of the lining of the heart), other types of vasculitis, severe Raynaud's phenomenon associated with connective tissue disorders (e.g., lupus or scleroderma), clotting disorders of the blood, and others.

Angiograms of the upper and lower extremities can be helpful in making the diagnosis of Buerger's disease. In the proper clinical setting, certain angiographic findings are diagnostic of Buerger's. These findings include a "corkscrew" appearance of arteries that result from vascular damage, particularly the arteries in the region of the wrists and ankles. Angiograms may also show occlusions (blockages) or stenoses (narrowings) in multiple areas of both the arms and legs.

Pictured below on the left is a normal angiogram. On the right, is an abnormal angiogram of an arm demonstrating the classic "corkscrew" appearance of arteries to the hand. The changes are particularly apparent in the blood vessels in the lower right hand portion of the picture (the ulnar artery distribution).



▲ normal angiogram ▲ abnormal angiogram

In order to rule out other forms of vasculitis (by excluding involvement of vascular regions atypical for Buerger's), it is sometimes necessary to perform angiograms of other body regions (e.g., a mesenteric angiogram).

Skin biopsies of affected extremities are rarely performed because of the frequent concern that a biopsy site near an area poorly perfused with blood will not heal well.

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Treatment and Course of Buerger's

It is essential that patients with Buerger's disease stop smoking immediately and completely. This is the only treatment known to be effective in Buerger's disease. Patients who continue to smoke are generally the ones who require amputation of fingers and toes.

Despite the clear presence of inflammation in this disorder, anti-inflammatory agents such as steroids have not been shown to be beneficial. Similarly, strategies of anticoagulation (thinning of the blood with aspirin or other agents to prevent clots) have not proven effective. **The only way to prevent the progression of the disease is to abstain from all tobacco products.**

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